NCERQA STAR GRANT ABSTRACT

Objectives/Hypothesis: Acute exposure to ozone (O_3) causes airway hyper-responsiveness (AHR). However, the mechanistic basis for O_3 induced AHR has not been established. O_3 may be a particularly important respiratory hazard for children. Despite the importance of AHR as one of the defining features of asthma, no studies of age related differences in O_3 induced AHR have been reported. Hence, the purpose of this proposal is to examine age related changes in O_3 induced AHR in mice and to determine the mechanistic basis for observed changes. We hypothesize that O_3 induced TNFα formation is required for AHR, and that O_3 causes more pronounced AHR in young than adult mice due to a more pronounced inflammatory response, resulting in part from an increased dose of O_3 in the younger animals despite inhalation of the same concentration, and in part from age related differences in TNFα formation.

Approach: In aim 1, we will measure, in mice aged 2 weeks through 26 weeks, the concentration and time related effects of O_3 on AHR using whole body plethysmography and conventional mechanics, and on histologic and biochemical indices of airway injury and inflammation. In each mouse used for these studies, we will also measure ventilation (V_E) during O_3 exposure in order to assess the actual O_3 dose. In aim 2, we will test the hypothesis that O_3 induced translocation of the nuclear transcription factor AP-1 and subsequent production of TNFα leads to AHR, In mice of various ages, we will measure effects of O_3 on AP-1 translocation by gel shift assay, TNFα mRNA by Northern blotting, TNFα release by enzyme immunoassay, and we will assess O_3 induced AHR in mice rendered mice unresponsive to TNFα either by genetic deletion of TNFα receptors, or by administration of a soluble TNFα receptor - IgG chimera.

Expected Results: Our preliminary data indicate that we can expect to see more pronounced O_3-induced AHR in young versus older mice. We also expect that adult mice will have lower specific V_E and will reduce V_E during O_3 exposure, whereas younger mice will not, resulting in a greater inhaled dose of O_3 in the younger animals. If our hypothesis is correct, we would expect to see no difference in AHR-O_3 _dose_-response curves between animals of different ages even though we see a leftward shift in the AHR-O_3 _concentration_-response curves in the younger animals. In addition, we expect to generate data indicating an important role for the cytokine TNFα in O_3 induced AHR. The data will be important in establishing guidelines for ambient O_3 concentrations in a susceptible population, children, and in making informed decisions about interventional type studies in children.

Supplemental Keywords: air, sensitive populations, dose-response, health effects, biology, pathology **.**